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General Medicine

GLYCATED HAEMOGLOBIN (HBA1C) AND ITS ASSOCIATION WITH ISCHAEMIC STROKE IN DIABETICS AND NON- DIABETICS.

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KEYWORDS :

INTRODUCTION

Stroke is a condition that results in high mortality rates and severe disabilities. Stroke is expected to be the second most important cause of mortality worldwide by 2020. Most stroke survivors can and do experience improvements in their functional abilities, but the amount, rate, timing, pattern, type, and ultimate outcome of the improvements differ across patients and situations.1 Stroke severity and patient age are the main predictors of stroke outcome in the acute phase 2. Additional important predictors include functional status prior to stroke, presence of comorbid medical conditions, etiologies and the vascular territories affected.3

Diabetes mellitus is one of the established risk factors for stroke. It has been demonstrated that diabetic patients had worse residual neurological deficits and functional outcome when compared with nondiabetic patients.4 Hyperglycemia occurred in up to one-third of patients with acute ischemic stroke and was associated with higher mortalities independent of age and stroke severity [5]. However, few studies have assessed the effects of prestroke glycemic control status on clinical outcomes in acute stroke patients. In a study published in 2011, the association between prestroke glycemic control status and neurological or functional outcomes was evaluated in 3,627 patients with first-ever ischemic stroke. It was suggested that the serum hemoglobin A1c level on admission was a significant independent predictor for clinical outcomes [6].

Hemoglobin A1c has a direct relationship with mean glycemia because erythrocytes are continuously glycated during their 120-day lifespan, which means that the rate of formation of glycated hemoglobin, also called HbA1c, is proportional to the ambient glucose concentration [7]. In the diabetes control and complication trial, an HbA1c of 6% corresponded to a mean serum glucose level of 135 mg/dL, and the measurement of HbA1c has been the primary index of glycemia [7]. An HbA1c test can be used to diagnose pre-diabetes or diabetes and check the long-term control of blood glucose levels in people with diabetes. Serum blood glucose level changes during the day for many reasons, including medicine, diet, exercise, and the level of insulin in the blood, while the HbA1c test result is not affected by any recent changes [8]. HbA1c is independent risk factor for diabetic complication, with the risks of macrovascular events, such as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, and death only clearly lower when down at levels of 7% [8].

Approximately 30% to 40% of acute ischemic stroke patients present with hyperglycemia at admission either as a result of preexisting diabetes mellitus or acute stress response. Type 2 diabetes, a disease that affects more than 220 million people worldwide, has an alarming number of new cases in the Asian population and holds a 2- to 6-fold increased risk for ischemic stroke. Moreover, hyperglycemia is associated with poor outcome in acute ischemic stroke. Thus, in recent years, there has been a growing interest in methods to manage hyperglycemia in acute ischemic stroke [9,10].
HbA1c level is widely recommended as the therapeutic guideline for the prevention of cardiovascular complications in patients with diabetes [11]. Recently published clinical practice recommendations from the American Diabetes Association advocate the use of a HbA1c level greater than 6.5% for the diagnosis of diabetes, largely on the basis of the established association between HbA1c level and microvascular complications. Compared with fasting glucose, HbA1c has higher repeatability, can be tested in a non-fasting status, and is a relatively stable marker for glucose level. The disadvantage of the use of HbA1c in the diagnosis of diabetes might be the fact that the measurement of HbA1c level is not standardized, which may result in unreliable values in different laboratories and countries [12].

Despite the recent impending increase in risk for diabetes and ischemic stroke in Asians, and the increasing importance of predictive value of HbA1c in future risk for cardiovascular disease, there are no studies that have investigated the association of ischemic stroke with HbA1c level in Asians. We cross-sectionally analyzed the risk for ischemic stroke according to HbA1c level in indian male patients admitted due to acute ischemic stroke without a previous history of diabetes

The socioeconomic prospects of Asia have recently taken a dramatic change including changes in lifestyle, diet and urban localisation. This has brought changes in risk of cardiovascular diseases especially stroke.13, 14 Prevalence of diabetes and prediabetes has increased in Asia including India in the past decade, nearly doubling during this era. 15,16,17 Diabetes and prediabetes both show increased risk for ischaemic stroke and are associated with poor patient outcomes.18,19 With the increased risk of diabetes and ischaemic stroke in Asians, the importance of predictive value of glycated haemoglobin (HbA1c) has been an area of active study in recent years.20,21

AIMS & OBJECTIVES

1. The aim of this study was to analyse the role of HbA1c in the risk prediction of ischaemic stroke in Indian population without diabetes.
2. We further studied the difference between HbA1c values of individuals with and without diabetes with stroke.

MATERIALS AND METHODS

This single centre, descriptive, case–control study was carried out on inpatients admitted to department of General Medicine, Meenakshi Medical College, kancheepuram for a period of 4 months from july 2019 to October 2019.All the patients of both genders ≥18 years of age were included in the study.

The study was approved by the institutional ethical committee and carried out in a tertiary care hospital.

Inclusion criteria

- Acute Ischemic stroke patients

Exclusion criteria

- Intra cerebral haemorrhage
- Space occupying lesions
- Sub arachnoid haemorrhage
- Cerebral venous thrombosis
- Transient ischemic attacks

- Patients with recurrent cerebrovascular events

A semi structured proforma was prepared which included socio demographic details, detailed history, clinical examination and requisite investigations available at meenakshi hospital. History includes all of the symptoms pertaining to the ischemic stroke in detail with emphasis on all the risk factors including the glycemic status at the time of admission.

HbA1c levels, fasting blood glucose levels, random blood glucose levels, lipid profiles and blood pressure (BP) were recorded for all individuals. HbA1c levels were recorded at the time of stroke when patients were initially admitted. Height and weight were measured and body mass index (BMI) was calculated by dividing the weight (kg) by the height (m2). Smoking history was noted. A total of 100 diabetics and 100 non diabetics were included in the study who fulfilled the inclusion criteria and gave informed consent.

All patients with stroke had suffered from focal symptoms of stroke and were observed within 1 week of symptom onset. The diagnosis of stroke was made by the Medicine consultant on the basis of history revealing focal symptoms, clinical examination supporting it and by neuroimaging ie, CT scan and/or MRI brain. Furthermore, patients with otherwise unclear or suspicious diagnosis of stroke were also not included for analysis. The following laboratory investigations were performed as a part of routine work up like complete blood counts, liver function tests, renal function tests, electrolytes, ECG, Chest X-ray, fasting blood sugar, random blood sugar,urine routine examination, echocardiography, coagulation profile, HbA1c and lipid profile. Lipid profile panel consisted of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride cholesterol (TGL-C) levels.

Criteria for diagnosis of diabetes mellitus was done following the criteria of American Diabetes Association (ADA, 2011); symptoms of diabetes plus random blood concentration³ 200 ml/dl or fasting plasma glucose 126 ml/dl or HbA1c > 6.5% or two-hour plasma glucose³ 200 ml/dl during an oral glucose tolerance test.

The plasma venous glucose level was taken within 24 hours after admission for every patient. Glycosylated haemoglobin (HbAIC) was done to ascertain whether it was stress diabetes or newly diagnosed diabetes. The patient with a raised blood glucose on admission and normal HbAIC level was considered as having stress hyperglycaemia. The patients were divided into 4 groups: euglycaemic patients with no history of diabetes having normal blood glucose and normal HbAIC concentration; patients with stress hyperglycaemia (no history of diabetes with normal HbAIC but raised blood sugar at admission); newly diagnosed diabetics (no history of diabetes, HbAIC greater than normal); and lastly, known diabetic patients.

The data was analysed using SPSS V.22.0. Descriptive analysis was carried out and reported as mean±SD for continuous variables whereas frequencies and percentages were calculated for categorical variables. A comparison was made between age, gender, BMI, smoking, FBS, HbA1c, HDL-C, LDL-C, TGL-C, TC, SBP and DBP values on a subset of patients in two groups; with diabetes versus without diabetes with ischaemic stroke. p Values <0.05 were considered statistically significant.

RESULTS

Out of the 200 patients, 56 cases (28%) of stroke occurred in the age group of 51 - 60 years; another 60 cases (26%) occurred in the age group of 61 - 70 years (Table I). This shows that the commonest age group is in the age group 50 - 70 years as detected by our study.

Table I: Age-wise distribution of patients.

Age groups in years	No. of patients Diabetics n	No. of patients Non Diabetics n	Total n (%)
Up to 40	5	3	**8 (4%)**
41 – 50	16	13	**29 (14.5%)**
51 – 60	37	19	**56 (28%)**
61 – 70	35	25	**60 (30%)**
Above 70	27	20	**47 (23.5%)**
Total	**100(50%)**	**100(50%)**	**200(100%)**

There are 63 cases of stroke with euglycaemia, 26 cases of stroke with hyperglycaemia including stress hyperglycaemia,11 newly detected diabetes, and 100 known diabetes. (Table II).

Table II: Classification of patients according to glycaemic status.

Glycaemic status	No. of cases	Percentage
Euglycaemic	**63**	**31.5%**
Hyperglycaemic	**26**	**13%**
New diabetic	**11**	**5.5%**
Known diabetic	**100**	**50%**
Total	**200**	**100%**

Mean age was 53.75 ± 1.77 (Range: 21–82) years in diabetes group and 58.51 ± 2.11
(Range: 23 – 86) in without diabetes group. Among the individuals with diabetes, 61 were males while 39 were females. Among individuals without diabetes, there were 54 males and 46 females. Mean age and gender were not statistically significantly different between the two groups. When HbA1c values were compared between individuals with diabetes and individuals without diabetes with stroke, mean HbA1c values were significantly higher in diabetes group (7.81±2.34 vs 6.23±2.17) (p<0.05) but other parameters were not statistically significantly different (p>0.05; Table III).

Table III : Comparison between individuals with diabetes and without diabetes with stroke

Variables	Individuals without diabetes (n=100)	Individuals with diabetes(n=100)	p Value
Age (years)	53.75 ± 1.77	58.51 ± 2.11	0.57
Gender/sex (males)	61	54	0.48
Gender/sex (females)	39	46	
FBS (mg/dL)	118.61±6.45	132.71±5.17	0.34
HbA1c (%)	6.23±2.17	7.81±2.34	<0.01
HDL-C (mg/dL)	46.93±2.29	44.92±5.67	0.67
LDL-C (mg/dL)	97.13±6.61	99.43±8.50	0.93
TGL-C (mg/dL)	163.43±31.24	185.12±24.56	0.55
TC (mg/dL)	164.50±24.60	177.65±25.21	0.35
SBP (mm Hg)	162.01±52.21	173.55±17.99	0.13
DBP (mm Hg)	89.12±18.16	94.17±8.41	0.16
BMI (kg/m2)	24.19±2.14	26.12±3.45	0.32

Comparison between individuals with diabetes and without diabetes with stroke: values are presented as mean ± SD.

BMI, body mass index; BSF, blood sugar fasting; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TGL-C, triglyceride
Cholesterol

DISCUSSION

Diabetes mellitus is a metabolic disease prevalent throughout the world and its burden has been increasing in developing and underdeveloped countries. The diversity of this disease varies greatly throughout the world in respect to cut-off values, prevalence and associations.

Prediabetes is an independent risk factor for stroke but most patients with acute stroke are not aware of whether or not they are prediabetic. HbA1c determination is currently accepted for prediabetes diagnoses.

HbA1c level is an indicator of mean glucose control in the previous 60–90 days in patients with or without diabetes mellitus. HbA1c level is a good diagnostic tool but is also helpful for prognosis and to monitor therapeutic effects of drugs in diabetes. Well controlled and steady blood glucose levels can help prevent cardiovascular complications in patients with diabetes mellitus.22

Current study showed that patients with ischaemic stroke had significantly higher mean HbA1c level (7.81±2.34 vs 6.23±2.17) (p<0.05) between Diabetics and Non diabetics.

Myint et al carried out a study on a population of more than 10 000 patients and found that 164 incident strokes after adjustment for confounding variables (age, sex and cardiovascular risk factors), the relative risks for stroke with HbA1c concentrations 5–5.4%, 5.5–6.9% and ≥7% were 0.7, 0.8 and 2.8, respectively, compared with those with HbA1c <5%.[23]

A Mexican study concluded that diabetes and prediabetes are highly prevalent in hospitalised patients with ischaemic stroke. They

suggested introducing the routine screening for diabetes and prediabetes via HbA1c testing in all patients with ischaemic stroke.[24]

LIMITATION

The limitation was that the diagnosis of diabetes was based on history, previous health records, levels of fasting glucose and HbA1c but glucose challenge test was not performed as a part of this study. Although recent guidelines recommend that fasting glucose and HbA1c levels are sufficient to diagnose diabetes, there is still a possibility that individuals with diabetes could have been missed.

CONCLUSION

Severity of stroke correlates with the glycaemic status of the patients in diabetics and non-diabetics. Hyperglycaemia, an important risk factor in non-diabetic patients after acute stroke is a stress response reflecting more severe neurological damage. Management of hyperglycaemia in patients with diabetes and non-diabetes is an important aspect of the emergency management of stroke.

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